#12

AMENDMENT

In the Claims:

Claim 10, line 1, change "11" to -- 1 --.

REMARKS

1. Claim 10 has been amended to correct a typographic error.

2. Response to the Withdraw of Rejection of Claims 1 to 29 based on 35 U.S.C. §112, first paragraph

Applicant appreciates the Examiner's consideration and withdraw of rejection of Claims 1 to 29 based on 35 U.S.C. §112, first paragraph. However, the Examiner mischaracterized Applicant's response to this rejection in the Response to the Office Action dated April 21, 2000 (Paper No. 6). The Examiner attributes to Applicant the statement that "the claimed invention is not intended to be used for gene therapy". Applicant respectfully points out that this statement is taken out of context from Applicant's response. The statement made by Applicant in Paper No. 6 is recited herein for the purpose of clarification:

> Applicant respectfully points out that the present claimed invention is to a method of producing a protein only in the progenitor cells of red blood cells, and delivering produced protein into blood stream by rupture of the red blood cells. From the blood stream, the protein can be delivered to the functional site, which can be directly in the circulating blood, as in the case of human serum albumin and insulin, or to specific organs and tissues. However, Applicant's claimed invention is not a mechanism of protein intake by a specific cell. Furthermore, although the present invention can be used for disease treatment as apparent to one skilled in the art, Applicant

claimed invention as defined by the claims is not, nor intended to be, a specific gene therapy protocol.

Applicant is only responsible for enablement of the disclosed method within the scope defined by the claims, not beyond the scope of the claims. As Examiner stated in the above citation (page 4, line 6 of the Office Action), the present invention is "enabling for delivery of a protein to the blood in vivo". That is precisely the claimed invention. Therefore, Applicant believes that the specification, as filed, satisfies the enablement requirement (emphasis is added).

Moreover, the Examiner improperly noted, "Applicant did not rebut the grounds of rejection with respect to enablement of gene therapy." Applicant respectfully disagrees with this conclusion. As stated in the recited second paragraph, Applicant is only responsible for enablement of the disclosed method within the scope defined by the claims, not beyond the scope of the claims. The Examiner understood and explicitly stated in the first Office Action that the present invention is "enabling for delivery of a protein to the blood in vivo". It is improper to apply the enablement requirement beyond the scope of the presently claimed invention.

Accordingly, the record shows that Applicant properly traversed the rejection according to scope of the presently claimed invention.

3. Response to Rejection of Dependent Claims 10 and 24 based on 35 U.S.C. §112, first paragraph

Dependent Claims 10 and 24 stand rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the Specification in such a way as to enable one skilled in the art to make and/or use the invention. More specifically, the Examiner asserts that the Specification teaches that the life cycle of red blood cells can be modified by genetic mutations, but teaches no mutations which would be suitable for this purpose and provides no guidance as to

how to obtain cells comprising these mutations. This rejection is respectfully traversed.

Claims 10 and 24, which depend from Claims 1 and 16 respectfully, are narrowed claims to a method of delivering proteins in which red blood cells containing the proteins are induced to rupture in vivo by genetic mutation.

Applicant disclosed in the specification as filed (page 12, line 2) that the life cycle time of red blood cells can be modified by genetic mutation. Applicant made such an example because it is known to those skilled in the art that genetic mutation can cause shortening of red blood cell life time. For instance, spherocytosis and elliptocytosis result from genetic mutation. In both spherocytosis and elliptocytosis, abnormally shaped red blood cells have a shorter lifetime. It is also known to those skilled in the art that mutations of red blood cell enzymes lead to haemolytic anemia.

Applicant submitted copies of two references regarding genetic mutations in Paper No. 6 to illustrate that genetic mutations resulting shortened red blood cell life was well known in the art at the time of filing. Moreover, the Examiner acknowledged that the submitted references "support the position that natural mutations resulting in shortened red blood cell life were well know in the art at the time of filing." Therefore, it is not necessary for Applicant to make available the known mutated genes.

Applicant merely utilized known genetic techniques for producing cells with mutated genes in the claimed inventive method for producing and delivering protein into the blood stream. Therefore, those skilled in the art at the time of the filing of the present patent application would have been able to produce the known mutated genes and cells, without undue experimentation, given the teachings of the Specification along with tools and methods well known in the art. Moreover, Applicant fully disclosed the method of introducing a non-native gene to the progenitor cells of red blood cells in the Specification and in the Example as filed, see page 7 to 9, and page 16 to 18. There would be no undue experimentation required to obtain Applicants claimed induced rupture of red blood cells by genetic mutation.

Accordingly, Applicant respectfully requests withdrawal of the rejection of Claims 10 and 24 based upon 35 U.S.C. §112, first paragraph.

4. Response to Rejection of Dependent Claims 10 and 24 based on 35 U.S.C. §112, second paragraph

Dependent Claims 10 and 24 stand rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. This rejection is respectfully traversed.

Claims 10 and 24 are dependent claims of Claim 1 and 16, respectively. Claims 1 is directed to a method for producing a non-native protein in the progenitor cells of red blood cells, and using red blood cell rupture to deliver produced protein into blood stream in vivo. Claim 16 is directed to a method using a hemoglobin promoter to produce a non-hemoglobin protein in the progenitor cells of red blood cells, and using red blood cell rupture to deliver produced protein into blood stream in vivo. Claims 10 and 24 further define the methods, as further embodiments of the present invention, wherein the red blood cell rupture can be induced by genetic mutation, which modifies the lifetime of the red blood cells.

The Examiner is respectfully requested to consider the holding in Beachcombers International, Inc. v. Wildewood Creative Products, Inc. 31 USPQ 2d 1653, 1656 (Fed. Cir. 1994) which held:

> The relevant statute, 35 U.S.C. §112 ¶ 2 (1988), requires that the claims "particularly [point] out and distinctly [claim] the subject matter which the applicant regards as his invention." The operative standard for determining whether this requirement has been met is "whether those skilled in the art would understand what is claimed when the claim is read in light of the specification." Orthokinetices Inc. v. Safety Travel Chairs Inc., 806 F.2d 1565, 1576, 1 USPQ 2d 1081, 1088 (Fed. Cir. 1986).

Claims 10 and 24 do in fact particularly point out and distinctly claim the subject matter, which Applicant regards as the invention. In the instant case, the

Examiner has failed to point out any disclosure in the Specification, which is inconsistent with Applicant's intention to claim the invention as recited in Claims 10 and 24. In addition, the Examiner has not provided any reason why one skilled in the art would not understand what is claimed when the claims are read in light of the Specification. Finally, the claims are not indefinite because the claims do not take on an unreasonable degree of uncertainty when construed in light of the prior art and the disclosure of the Specification.

In In re Tanksley, 37 USPQ 2d 1382, 1386 B.P.A.I. 1994) the Board held:

> In our judgement, a patent applicant is entitled to a reasonable degree of latitude in complying with the second paragraph of 35 U.S. C. §112 and the examiner may not dictate the literal terms of the claims...Stated another way, a patent applicant must comply with 35 U.S.C. §112, second paragraph, but just how the applicant does so, within reason, is within applicant's discretion.

To conclude, the Examiner asserted that Claims 10 and 24 are incomplete for omitting essential steps, such omission amounting to a gap between the steps. However, as discussed above in section 4, since genetic mutations resulting in shortened red blood cell life is well known in the art at the time of filing, it is readily known by one skilled in the art to introduce into the cell a gene of a protein which is known to shorten the red blood cell life cycle to facilitate earlier rupture of the red blood cells. Furthermore, Applicant fully disclosed the method of introducing a non-native gene to the progenitor cells of red blood cells. In conclusion, Applicant believe that the holding in Stiftung v. Renishaw plc, 20 USPQ 2d 1094, 1101 (Fed. Cir. 1991) is dispositive of this rejection wherein the Court stated:

> It has long been held, and we today reaffirm, that it is entirely consistent with the claim definiteness requirement of the second paragraph of section 112, to present "subcombinations" claims, drawn to only one aspect or combination of elements of an invention

> that has separate utility and apart from other aspects of the invention...[I]t is not necessary that a claim recite each and every element needed for the practical utilization of the claimed subject matter.

Accordingly, Applicant respectfully requests withdrawal of the rejection of Claims 10 and 24 based upon 35 U.S.C. §112, second paragraph.

5. Response to Rejection of Claims 1, 3, 5, 8, 9, 16-18, 22, 23, and 27 based upon 35 U.S.C. §102(b)

Claims 1, 3, 5, 8, 9, 16-18, 22, 23, and 27 stand rejected under 35 U.S.C. §102(b) as being anticipated by Hollis et al (US Patent 5,538,885). This rejection is respectfully traversed.

Hollis et al teach expression systems which comprise a mammalian host transformed with a vector which comprises a promoter, and a DNA sequence which codes for a desired polypeptide and a dominant control region. Further, Hollis et al teach that the expression systems are capable of expressing a polypeptide at high levels and secreting the polypeptide expressed.

More specifically, Hollis et al demonstrate in Example 3 the long term secretion of human growth hormone (HGH) over a period of 80 days in vitro (column 14, line 47 to column 15, line 25). To confirm the mechanism of the protein delivery, Hollis et al further demonstrate in Example 4 that no increase in supernatant HGH levels in the presence of a secretion inhibitor, brefeldin-A, which is known specifically blocking flux through the Golgi apparatus. Hollis et al conclude, therefore, that "the appearance of HGH in the supernatant is due to the secretion of the protein through the Golgi apparatus".

Applicant's claimed invention is a method for producing and delivering protein in vivo, which comprises inserting a promoter and a gene encoding a non-native protein to red blood cells in a vector, wherein the promoter is active only in the progenitor cells of red blood cells; collecting an amount of progenitor cells of red blood cells from a mammal; treating the progenitor cells of red blood cells in vitro with

the vector; introducing the treated progenitor cells of red blood cells back to the mammal, wherein the treated progenitor cells of red blood cells produce red blood cells and the protein in vivo in the mammal, and wherein the protein is contained only in the red blood cells, and thereafter the protein is released into blood stream of the mammal through rupture of the red blood cells.

Hollis et al is a deficient reference because Hollis et al fail to teach Applicant's claimed delivery mechanism which utilizes rupture of the red blood cells for delivering produced protein into blood stream in vivo. Most importantly, Hollis et al teach away from the Applicant's claimed invention. As discussed above, Hollis et al confirmed experimentally that the protein delivery mechanism of their expression system is cell secretion. Therefore, Hollis et al teach that the natural result flowing from the operation as taught would result in the performance of secretion. This teaching is contrary to Applicant's claimed invention.

The Examiner agrees that Hollis et al do not teach that the red blood cells should lyse and release the protein into the blood. However, the Examiner alleges lysis of red blood cells is an inherent property, therefore, Hollis et al anticipates the Applicant's claims. Applicant respectfully disagrees.

Applicant specifically discussed in the Specification as filed and restated in Paper No. 6 that there are two known pathways for proteins to export from the cells after their production. The first pathway is secretion. The second pathway is exocytosis. Both processes are natural processes of protein exportation. Applicant's claimed invention is materially different from these two processes and delivers the expressed proteins into blood stream through red blood cell rupture.

As held by the Court in In re Weiss, 26 USPQ 2d 1885, 1888 (Fed. Cr. 1993):

> The mere fact that a certain thing may result from a given set of circumstances is not sufficient [to establish inherency]...[which requires that] the disclosure is sufficient to show that the natural results flowing from the operation as taught would result in the performance of the questioned function.

Nothing in Hollis et al would teach one skilled in the art that the natural result flowing from the Hollis et al's protein secretion mechanism would result in Applicant's claimed rupture of red blood cells.

Moreover, Hollis et al cannot be found to disclose Applicant's claimed red blood cell rupture by virtue of its inherency because one of ordinary skill in the art viewing the Hollis et al reference teaching secretion of protein would not understand that the unmentioned feature of protein delivery by red blood cell rupture is present in the Hollis et al reference.

In addition, Hollis et al's teaching relies solely on cell secretion for protein delivery regardless the expression systems. It is apparent from Hollis et al's teaching that rupture of red blood cells has not been utilized for a mechanism of protein delivery by the instant prior art. With respect to inherency, W.L. Gore Associates Inc. v. Garlock, 220 USPQ 303, 314 (Fed Cir. 1983), cert. Denied, 469 U.S. 851 (1984) stands for the principal that inherency may be relied upon only where the consequence of following the reference disclosure always inherently produces or results in the claimed invention. In the present situation, the consequences of following Hollis et al. does not always produce or results in Applicant's claimed invention.

For all the reasons given above, Hollis et al fail to anticipate Applicant's claimed invention. Accordingly, Applicant respectfully requests withdrawal of the rejection based upon 35 USC §102(b).

6. Response to Rejection of Claims 1, 4, 16, and 19 based upon 35 U.S.C. §103 (a)

Claims 1, 4, 16, and 19 stand rejected under 35 U.S.C. §103 (a) as being unpatentable over Hollis et al (US Patent 5,538,885), Rixon et al (Mol. Cell. Biol. 8(2): 713-721, 1988), and Zhang et al (Shengwu Huaxue Zazhi 11(3): 343-347, 1995). This rejection is respectfully traversed.

Claim 1 and 16 are independent claims with different claim limitations. Claim 1 is directed to a method for producing a non-native protein in the progenitor cells of red blood cells, and using red blood cell rupture to deliver produced protein into blood

stream in vivo. Claim 16 is directed to a method using a hemoglobin promoter to produce a non-hemoglobin protein in the progenitor cells of red blood cells, and using red blood cell rupture to deliver produced protein into blood stream in vivo. Claims 4 and 19 are dependent claims of Claims 1 and 16, respectively.

Hollis et al's has been discussed above. The deficiencies of Hollis et al are not overcome by Rixon et al and Zhang et al.

Rixon et al teach a mutated hemoglobin promoter having increased activity relative to the wild type. Rixon et al's teaching addresses efficiency of gene expression, however, it does not address the issue of delivery of a gene expression product to its functional site after its production as claimed by Applicant.

Zhang et al. also teach mutated hemoglobin promoter taught by Rixon having increased activity relative to the wild type. Again, Zhang et al 's teaching only addresses efficiency of gene expression. More specifically, in the suggested appropriate applications, the descendent cells of hematopoitic stem cells are actual functional site of the gene expression product. The hemoglobin produced in such method only functions in red blood cells, and there is no need to deliver the protein outside of red blood cells.

Both Rixon et al. and Zhang et al fail to teach producing a non-native protein, or using hemoglobin promoter to produce non-hemoglobin proteins only in the progenitor cells of red blood cells, and delivering the gene expression product into blood stream in vivo through rupture of red blood cells.

Viewing all the teachings of the prior art presented, the inventive concept of Applicant's claimed invention is missing. Therefore, Rixon et al. and Zhang et al. fail to overcome the deficiencies of Hollis et al. Viewing all the teachings of the prior art presented, one of ordinary skill in the art would not have expected to be able to modify or combine Hollis, Rixon, and Zhang references to obtain Applicant's claimed invention.

Furthermore, the citation of many references by the Examiner, none showing a delivery method through a non-secretion mechanism, is persuasive evidence of Applicant's claimed invention.

Accordingly, Applicant respectfully requests withdrawal of the rejection based upon 35 U.S.C. §103(a).

7. Response to Rejection of Claims 1, 6, 7, 16, 20, and 21 based upon 35 U.S.C. §103 (a)

Claims 1, 6, 7, 16, 20, and 21 stand rejected under 35 U.S.C. §103 (a) as being unpatentable over Hollis et al (US Patent 5,538,885), Schlegel (US Patent 5,576,206), and Wickham et al (US Patent 5,846,782). This rejection is respectfully traversed.

Applicant's claimed invention defined by Claims 1 and 16 are discussed above. Claims 6, 7, 20, and 21 are dependent on Claims 1, and 16, respectively, which further define the vectors used for expressing proteins.

Hollis et al's teaching has been discussed above. The deficiencies of Hollis et at are not overcome by Schlegel and Wickham et al.

Schlegel teaches a process of immortalizing cells to produce immortalized cell lines. Further, Schlegel teaches that the immortalized cells are either actual functional sites of the gene expression product, or they export the product through secretion, which is contrary to Applicant's claimed invention.

Wickham teaches a chimeric adenovirus fiber protein, vectors that comprise the chimeric adenovirus fiber protein, and the methods of constructing and using such vectors. Wickham's teaching provides improved vectors and methods for cell targeting. However, Wickham's teaching only addresses efficiency of protein production by improving vectors and methods for cell targeting, it does not address protein delivery after its production.

Both Schlegel and Wickham et al. fail to teach producing a non-native protein, or using hemoglobin promoter to produce non-hemoglobin proteins only in the progenitor cells of red blood cells, and delivering the gene expression product into blood stream in vivo through rupture of red blood cells.

Viewing all the teachings of the prior art presented, the inventive concept of Applicant's claimed invention is missing. Consequently, using retroviral or adenoviral

vectors by Schlegel and using lentiviral vector by Wickham for gene expression are not relevant to Applicant's claimed invention. Therefore, the deficiencies of Hollis et al are not overcome by the Examiner's picking and choosing of selected teachings from the additional references of Schlegel and Wickham.

In conclusion, viewing all the teachings of the prior art presented, one of ordinary skill in the art would not have expected to be able to modify or combine Hollis, Schlegel, and Wickham references to obtain Applicant's claimed invention.

Accordingly, Applicant respectfully requests withdrawal of the rejection based upon 35 U.S.C. §103(a).

8. Response to Rejection of Claims 1, 11-16, 25 and 26 based upon 35 U.S.C. §103 (a)

Claims 1, 11-16, and 26 stand rejected under 35 U.S.C. §103 (a) as being unpatentable over Hollis et al (US Patent 5,538,885), Schlegel (US Patent 5,576,206), and Chatterjee et al (US Patent 5,935,821). This rejection is respectfully traversed.

Applicant's claimed invention defined by Claims 1 and 16 are discussed above. Claims 11-15, and 25-26 are dependent on Claims 1, and 16, respectively, which further define the proteins produced using the method of the present invention.

Hollis et al's and Schlegel's teachings have been discussed above. The deficiencies of Hollis et at and Schlegel are not overcome by Chatterjee et al.

Chatterjee et al teach genetic immunization by expressing nucleic acid encoding an antibody. Chatterjee et al also teach that exportation of the expression product relies on cells' natural secretion.

Chatterjee et al fail to teach producing a non-native protein, or using hemoglobin promoter to produce non-hemoglobin proteins only in the progenitor cells of red blood cells, and delivering the gene expression product into blood stream in vivo through rupture of red blood cells.

Viewing all the teachings of the prior art presented, one of ordinary skill in the art would not have expected to be able to modify or combine Hollis, Schelgel, and Chatterjee references to obtain Applicant's claimed invention.

Importantly, Applicant respectfully points out that the citation of many prior references by the Examiner, none showing a protein delivery method through a non-secretion mechanism, is persuasive evidence of Applicant's invention.

On the other hand, it has been a long felt need for solutions to the problem of production and delivery of protein in vivo. New strategies and methods to overcome difficulties in achieving the goals of producing and delivering proteins in vivo are strongly in demand. The fact that lack of teaching in the art, either patents or scientific publications, on using Applicant's approach for protein production and delivery in vivo strongly indicates unobviousness of Applicant's claimed invention. Accordingly, Applicant respectfully requests withdrawal of the rejection based upon 35 U.S.C. §103(a).

9. Request of Withdraw Finality of the Office Action

The Examiner did not address the previous rejections under 35 U.S.C. §102(b) based on Schlegel. Therefore, Applicant understands that this rejection in the first Office Action has been overcome.

In the instant Office Action, the Examiner made one rejection under 35 U.S.C. §102(b) and three rejections under §103(a) based upon a newly cited art, Hollis et al (US Patent 5,538,885). Hollis et al was prior art not of record, and was not submitted in an information disclosure statement filed.

Therefore, Applicant respectfully submits that the finality of the Office Action is premature and improper according to MPEP 706.07(a).

The following is a citation of MPEP 706.07(a):

> ... a second or any subsequent action on the merits in any application or ... will not be made final if it includes a rejection, on newly cited art, other than information submitted in an information disclosure statement filed.....

> A second or any subsequent action on the merits in any application or ... should not be made final if it includes a rejection, on prior art not of record, of any claim amended to include limitations which should reasonably have been expected to be claimed. (emphasis added)

Moreover, Applicant respectfully points out that amended Claims 1, 8, 10, 16, and 24, made by Applicant in responding to the first Office Action in Paper No. 6, are narrower in scope than the corresponding claims as filed. These amendments were made with support of antecedent basis in the specification as filed. Specifically, the antecedent basis of amended Claims 1 and 8 can be found on page 8, line 25, and on page 7, line 21 to 22. The antecedent basis of amended Claims 10 and 24 can be found on page 12, line 3.

The Examiner stated in the conclusion that "Applicant's amendment necessitated the new grounds of rejection present in this Office action. Accordingly, this action is made final". Applicant strongly disagrees that Applicant's amendment necessitated the new grounds of rejection, because the limitations of the amended claims are within the scope of the claims as filed and should have been reasonably expected to be claimed.

More importantly, since the Examiner cited the new prior art not of record, not necessitated by Applicant's amendment, Applicant strongly believes that the finality of the Office Action is premature and improper. Therefore, Applicant respectfully requests withdraw of finality of the Office Action.

Additionally, Applicant respectfully points out that Claims 28 and 29 were not addressed in the Office Action. Applicant discussed status of these two claims with the Examiner during the telephone interview, whether they were allowable, or being rejected. Examiner said he would address this matter in the subsequently reissued Office Action, which was not sent out by the Patent and Trademark Office before the six month statutory deadline. Therefore, Applicant has not addressed Claims 28 and 29 in this response.

It is respectfully submitted that Claims 1-29 are now in condition for allowance and such action is respectfully submitted. Applicant's representatives respectfully requests direct telephone communication from the Examiner with a view toward any

further action deemed necessary to place the application in final condition for allowance.

3/27/2001
Date of Signature

By: _____

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